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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/615,497	HUANG, DOUG HUI	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *33-35 and 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-32,36-42 and 44-46* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0607*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL REJECTION

1. This action is responsive to the Response and Amendment including a complying complete set of claims filed August 31, 2007. Please note that the substitution specification filed August 31, 2007 has **not** been entered (see paragraphs 6 and 7, below).

Claims 1, 3-4, 6, 8, 12-13, 15, 19-22, 24, 26-28, 32, 36, 38-39, 41, and 44-45 have been amended and claim 46 has been added. Claims 33-35 and 43 remain withdrawn (see paragraphs 3 and 4, below). Claims 1-32, 36-42, and 44-46 are now under consideration. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and/or objections not reiterated in this action have been withdrawn. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

3. Claims 33-35 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 3, 2006.

4. Applicant's election with traverse of the polymorphisms CYP2D6*4, CYP2D6*5, and CYP2D6*Nx2 (and corresponding phenotypes) and of corresponding primers SEQ ID Nos 9, 14, and 11 in the reply filed on May 9, 2006 is again acknowledged. In a supplemental response filed August 3, 2006, Applicant clarified that the claims readable on the elected invention are claims 1-32, 36-42, and 44-45. Accordingly, Claim 43 is

withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 9, 2006.

5. This application contains claims drawn to an invention nonelected with traverse in the reply filed on May 9, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Specification

6. The substitute specification filed August 31, 2007 has not been entered because it does not conform to 37 CFR 1.125(b) and (c) because: the statement as to a lack of new matter under 37 CFR 1.125(b) is missing.

7. In accordance with MPEP 714.20, the substitute specification of August 31, 2007 has been denied entry; however, the claim amendments and response of August 31, 2007 (which contain no defects) have been entered and considered. It is also noted that the substitute specification provided by applicant has been inspected and (with the exception of the missing statement noted in the preceding paragraph) appears to be compliant.

Information Disclosure Statement

8. Regarding the IDS filed August 31, 2007, it is noted that the examiner has considered US 6,660,478 B1, which is disclosed by applicant as being the English language equivalent of WO 00/66775.

Claim Rejections - 35 USC § 112, second paragraph

9. Claims 19-32, 36-42 and 44-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons set forth below and in the prior Office action of November 1, 2006.

Claims 36-42 and 44-45 remain indefinite over the recitation of the limitation "at least one of a preselected polymorphism" in claim 36. It is not clear whether this language is intended to refer to, e.g., multiple copies of a single polymorphism, or whether applicant's intent was to recite "at least one preselected polymorphism," etc. The response did not traverse the rejection, and no clarifying amendment to the claims was made. This rejection is maintained.

Claims 36-42 and 44-45 remain indefinite over the recitation of the limitation "said preselected polymorphisms" because there is insufficient antecedent basis for the limitation in the claims. The response did not traverse the rejection, and no clarifying amendment to the claims was made. This rejection is maintained.

Claims 30-32 and 46 are indefinite because it is unclear how the claims further limit claims 1 and/or 19. Claims 30-31 each refer to "a cytochrome P450 2D6 genotype of said subject identified by the method of claim 1 or 19." However, as claims 1 and 19 are not drawn to identification of either a genotype or a subject, it is not clear how claims 30-32 further limit the methods of claims 1/19. The response did not traverse the rejection, and no clarifying amendment to the claims was made. **It is noted that**

applicant's amendment adding new claim 46 necessitated the inclusion of that claim in this rejection. This rejection is maintained.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S AMENDMENTS TO THE CLAIMS:

Claims 19-32 and 46 are indefinite over the recitation of the limitation "the distinctively labeled ddNTP" in the "generating" step of claim 19. It is noted that the claim previously refers to "distinctively labeled ddNTPs," but not to a single particular ddNTP. It is therefore not clear whether the "generating" step requires the previously referenced "distinctively labeled ddNTPs," or whether the step would encompass any one of (or a particular one of) the "distinctively labeled ddNTPs."

Claims 19-32 and 46 are indefinite over the recitation of the limitation "the labeled extension primers" in the "subjecting" step of claim 19. The claim previously refers to "at least one labeled extension primer" but not to multiple labeled extension primers. It is not clear whether the language of the "subjecting" step is intended to refer to the previously recited "at least one labeled extension primer" or whether the step actually requires that multiple, "labeled extension primers" be produced. Clarification is required.

Claims 19-32 and 46 are indefinite because the text of the "using" step of claim 19 refers to "a sample" rather than "the sample" or "said sample." As a result, it is not clear whether or how the "using" step relates to the other method steps of the claims.

Claim 26 is indefinite over the recitation of the limitation "said plurality of preselected cytochrome polymorphisms in said P450 2D6 gene" because there is insufficient antecedent basis for this limitation in the claims.

Claims 27-28 are indefinite over the recitation of the limitation "said preselected cytochrome polymorphisms in said P450 2D6 gene" in claim 27 because there is insufficient antecedent basis for this limitation in the claims.

Claim 28 is indefinite over the recitation of the limitation "selected from the group consisting of comprises" because it is not clear what sequence or sequences would be encompassed by this language. It is noted that the confusing claim language appears to result from a typographical error.

Claims 36-42 and 44-45 are indefinite over the recitation of the limitations "said distinctively labeled ddNTPs comprising a label" and "the said at least one of a plurality of preselected polymorphisms" because there is insufficient antecedent basis for these limitations in the claims.

Claim 38 is indefinite over the recitation of the limitation "said plurality of extension primers" because there is insufficient antecedent basis for this limitation in the claims.

Claim 45 is indefinite over the recitation of the limitation "said extension primers" because there is insufficient antecedent basis for this limitation in the claims.

Claim Rejections - 35 USC § 102

10. Claims 1-2, 4, 6-9, 11-20, 22, 24-27, 29-32 and 46 are rejected under 35 U.S.C. 102(e) as being anticipated by Anastasio et al (WO 02/38589 A2 [05/16/2002;

filed 11/09/2001]), in light of the teachings of Goelet et al (WO 92/15712 [09/17/1992]), for the reasons stated below and in the Office action of November 1, 2006. **Applicant's amendments to the claims necessitated any new grounds of rejection set forth herein, including the rejection of new claim 46.**

It is noted that the portions of the Anastasio et al reference on which the instant rejection relies find support in provisional application 60/247,943, filed November 9, 2000.

Anastasio et al disclose methods of genotyping and haplotyping the CYP2D6 gene in which one or more of the polymorphisms present in the gene are detected (see entire reference). Anastasio et al disclose methods in which primer extension is employed to identify polymorphisms, and disclose "primer extension oligonucleotides" for use in their methods in which the 3' termini of the oligonucleotides are "complementary to the nucleotide located immediately adjacent to the polymorphism site" (see, e.g., pages 18 and 22-23, and claim 4). In these methods of Anastasio et al, isolated nucleic acids from an individual are amplified, and primer extension is performed on the amplified nucleic acids, wherein the identity of the terminator in the extended oligonucleotide is identified to determine the identity of the polymorphism(s) present (see, e.g., claim 4). While Anastasio et al do not refer to the use of "distinctively labeled ddNTPs" in their methods (as set forth in independent claim 1), Anastasio et al do disclose the use of the "polymerase-mediated primer extension method" of patent WO92/15712 (Goelet et al) in the identification of polymorphisms (page 23). Goelet et al teach that their method employs differently labeled terminators, such that the

identification of the nucleotide at the position of interest may be established based on the identity of the detectable marker incorporated into the primer during extension (see entire reference, particularly pages 10-13 and 21-22, summarizing the primer extension method of Goelet et al). Thus, the Goelet et al reference provides extrinsic evidence that the primer extension method of Anastasio et al meets the limitations of, and anticipates, the claimed invention (see *MPEP* 2131.01).

With regard to independent claim 19 as amended, and claims dependent therefrom, the claims as amended merely require identification of "at least one polymorphism" using "at least one labeled extension primer," such that the claims broadly encompass methods in which the steps of the claims are practiced to achieve identification of only a single polymorphism. However, it is noted that Anastasio et al disclose the practice of primer extension assays on arrays in order to detect multiple polymorphisms "at the same time" (see page 19), as well as the use of sets of primer pairs to assay multiple polymorphic sites by primer extension (see page 22), and the investigation of "multiple polymorphic sites...simultaneously" (page 23). Further, Goelet et al disclose that primer extension involves the use of 4 differently labeled ddNTPs (see page 11), and also provide teachings of how primer extension may be performed to analyze "one or more specified positions" wherein "different positions can be determined simultaneously" (see, page 12, as well as pages 31-33). With regard to the method step requiring size separation and "using the length of the labeled extension primer and the identity of its distinctively labeled ddNTP to identify at least one polymorphism" (see text of claim 19), Goelet et al further teach that their method

encompasses subjecting labeled, extended primers to polyacrylamide gel electrophoresis (see, e.g., page 38 and 43), such that the method of Anastasio et al in light of Goelet et al would inherently include steps meeting the requirements of the claims (and further, it is again noted that the identification of only a single polymorphism is sufficient to meet the requirements of the claims, such that no actual teaching of the differentiation of the lengths of various products is actually required).

Regarding dependent claims 2 and 20, it is again noted that Anastasio et al disclose obtaining nucleic acids from a sample by amplification (see above).

Regarding dependent claims 4 and 22, it is noted that the method of Goelet et al (i.e., the method referenced in the Anastasio et al reference) requires identification of the detectable marker present on the terminator incorporated during primer extension (see, e.g., pages 11 and 22), and that Goelet et al teach subjecting labeled, extended primers to polyacrylamide gel electrophoresis (see, e.g., page 38 and 43).

With respect to claims 6 and 24, Goelet et al disclose automated methods (see, e.g., page 51-52).

Regarding claims 7 and 25, Goelet et al disclose the labeling of each terminator with a different fluorophore (see, e.g., page 20).

Regarding claims 8-9, 18, 26-27, 32, and new claim 46, Anastasio et al disclose more than 40 polymorphisms of the CYP2D6 gene, including multiple polymorphisms encompassed by the claims, and disclose detection of numerous haplotypes/genotypes of CYP2D6, including the wild type gene (see entire reference). With regard to the polymorphisms elected by applicant, it is particularly noted that the polymorphism

identified by Anastasio et al as "PS33" corresponds to CYP2D6*4 (see, e.g., page 4 and Figure 1B).

Regarding claims 12-17, 30-32, and new claim 46, Anastasio et al disclose that CYP2D6 is a "pharmaceutically-important" gene whose gene product is involved in metabolism of a variety of drugs including "antiarythmics; adrenoceptor antagonists, and trycyclic antidepressants," and teach that CYP2D6 genotype affects the extent to which a variety of drugs are metabolized in subjects (see, e.g., pages 1-3). With further regard to claims 30-32 and 46, Anastasio et al also teach the use of their genotyping/haplotyping methods in selecting appropriate drugs for treatment of a disease or condition (see, e.g., pages 7, 26-27).

Regarding claims 11 and 29, it is noted that the samples disclosed by Anastasio et al are human samples (see entire reference, particularly, e.g., the examples).

The response traverses the rejection on the following grounds. First, the response argues that "Neither Anastasio or Goelet describe a single reaction for P450 2D6 polymorphism detection that uses multiple extension primers and distinctively labeled ddNTPs." This argument has been thoroughly considered but is not persuasive. Goelet et al clearly teach that the method employed by Anastasio et al encompasses the use of multiple distinctly labeled ddNTPs in their methods (as previously noted, see page 11 of Goelet et al), and both references disclose the simultaneous analysis of multiple polymorphisms, which methods inherently involve the use of multiple extension primers (see, e.g., the discussion with regard to amended claim 19 set forth above). The response further argues that the references fail "to disclose a single reaction for

P450 2D6 polymorphism detection that uses multiple extension primers, wherein the primer for each polymorphism differs in length, and further includes distinctively labeled ddNTPs." However, Anastasio et al in view of Goelet et al do in fact teach the use of multiple extension primers and distinctively labeled ddNTPs in a single reaction, as noted above (see discussion of amended claim 19). Further, as the claims merely require the detection of "at least one polymorphism" using "at least one labeled extension primer," the claims as written do not actually require the use of multiple primers that differ in length for each polymorphism. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Accordingly, applicant's arguments are not persuasive.

Anastasio et al (in light of Goelet et al) teaches all the limitations recited in present claims 1-2, 4, 6-9, 11-20, 22, 24-27, 29-32 and 46, and therefore this rejection is maintained.

11. Claims 1-2, 4, 6-9, 11-20, 22, 24-27, 29-32 and 46 are rejected under 35 U.S.C. 102(a) as being anticipated by Anastasio et al (WO 02/38589 A2 [05/16/2002; filed 11/09/2001]), in light of the teachings of Goelet et al (WO 92/15712 [09/17/1992]), for the reasons stated below and in the Office action of November 1, 2006. **Applicant's amendments to the claims necessitated any new grounds of rejection set forth herein, including the rejection of new claim 46.**

Anastasio et al disclose methods of genotyping and haplotyping the CYP2D6 gene in which one or more of the polymorphisms present in the gene are detected (see

entire reference). Anastasio et al disclose methods in which primer extension is employed to identify polymorphisms, and disclose "primer extension oligonucleotides" for use in their methods in which the 3' termini of the oligonucleotides are "complementary to the nucleotide located immediately adjacent to the polymorphism site" (see, e.g., pages 18 and 22-23, and claim 4). In these methods of Anastasio et al, isolated nucleic acids from an individual are amplified, and primer extension is performed on the amplified nucleic acids, wherein the identity of the terminator in the extended oligonucleotide is identified to determine the identity of the polymorphism(s) present (see, e.g., claim 4). While Anastasio et al do not refer to the use of "distinctively labeled ddNTPs" in their methods (as set forth in independent claim 1), Anastasio et al do disclose the use of the "polymerase-mediated primer extension method" of patent WO92/15712 (Goelet et al) in the identification of polymorphisms (page 23). Goelet et al teach that their method employs differently labeled terminators, such that the identification of the nucleotide at the position of interest may be established based on the identity of the detectable marker incorporated into the primer during extension (see entire reference, particularly pages 10-13 and 21-22, summarizing the primer extension method of Goelet et al). Thus, the Goelet et al reference provides extrinsic evidence that the primer extension method of Anastasio et al meets the limitations of, and anticipates, the claimed invention (see *MPEP* 2131.01).

With regard to independent claim 19 as amended, and claims dependent therefrom, the claims as amended merely require identification of "at least one polymorphism" using "at least one labeled extension primer," such that the claims

broadly encompass methods in which the steps of the claims are practiced to achieve identification of only a single polymorphism. However, it is noted that Anastasio et al disclose the practice of primer extension assays on arrays in order to detect multiple polymorphisms "at the same time" (see page 19), as well as the use of sets of primer pairs to assay multiple polymorphic sites by primer extension (see page 22), and the investigation of "multiple polymorphic sites...simultaneously" (page 23). Further, Goelet et al disclose that primer extension involves the use of 4 differently labeled ddNTPs (see page 11), and also provide teachings of how primer extension may be performed to analyze "one or more specified positions" wherein "different positions can be determined simultaneously" (see, page 12, as well as pages 31-33). With regard to the method step requiring size separation and "using the length of the labeled extension primer and the identity of its distinctively labeled ddNTP to identify at least one polymorphism" (see text of claim 19), Goelet et al further teach that their method encompasses subjecting labeled, extended primers to polyacrylamide gel electrophoresis (see, e.g., page 38 and 43), such that the method of Anastasio et al in light of Goelet et al would inherently include steps meeting the requirements of the claims (and further, it is again noted that the identification of only a single polymorphism is sufficient to meet the requirements of the claims, such that no actual teaching of the differentiation of the lengths of various products is actually required).

Regarding dependent claims 2 and 20, it is again noted that Anastasio et al disclose obtaining nucleic acids from a sample by amplification (see above).

Regarding dependent claims 4 and 22, it is noted that the method of Goelet et al (i.e., the method referenced in the Anastasio et al reference) requires identification of the detectable marker present on the terminator incorporated during primer extension (see, e.g., pages 11 and 22), and that Goelet et al teach subjecting labeled, extended primers to polyacrylamide gel electrophoresis (see, e.g., page 38 and 43).

With respect to claims 6 and 24, Goelet et al disclose automated methods (see, e.g., page 51-52).

Regarding claims 7 and 25, Goelet et al disclose the labeling of each terminator with a different fluorophore (see, e.g., page 20).

Regarding claims 8-9, 18, 26-27, 32, and new claim 46, Anastasio et al disclose more than 40 polymorphisms of the CYP2D6 gene, including multiple polymorphisms encompassed by the claims, and disclose detection of numerous haplotypes/genotypes of CYP2D6, including the wild type gene (see entire reference). With regard to the polymorphisms elected by applicant, it is particularly noted that the polymorphism identified by Anastasio et al as "PS33" corresponds to CYP2D6*4 (see, e.g., page 4 and Figure 1B).

Regarding claims 12-17, 30-32, and new claim 46, Anastasio et al disclose that CYP2D6 is a "pharmaceutically-important" gene whose gene product is involved in metabolism of a variety of drugs including "antiarythmics, adrenoceptor antagonists, and trycyclic antidepressants," and teach that CYP2D6 genotype affects the extent to which a variety of drugs are metabolized in subjects (see, e.g., pages 1-3). With further regard to claims 30-32 and 46, Anastasio et al also teach the use of their

genotyping/haplotyping methods in selecting appropriate drugs for treatment of a disease or condition (see, e.g., pages 7, 26-27).

Regarding claims 11 and 29, it is noted that the samples disclosed by Anastasio et al are human samples (see entire reference, particularly, e.g., the examples).

The response traverses the rejection for the same reasons discussed in paragraph 10, above. Accordingly, the response to those arguments applies equally herein.

Anastasio et al (in light of Goelet et al) teaches all the limitations recited in present claims 1-2, 4, 6-9, 11-20, 22, 24-27, 29-32 and 46, and therefore this rejection is maintained.

Claim Rejections - 35 USC § 103

12. Claims 5 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anastasio et al in view of Dovichi and Zhang (Methods in Molecular Biology 167:225-239 [2001]; citation A20 of the IDS of 02/2004), in light of the teachings of Goelet et al, for the reasons stated below and in the Office action of November 1, 2006. **Applicant's amendments to the claims necessitated any new grounds of rejection set forth herein.**

Anastasio et al disclose methods of genotyping and haplotyping the CYP2D6 gene in which one or more of the polymorphisms present in the gene are detected (see entire reference). Anastasio et al disclose methods in which primer extension is employed to identify polymorphisms, and disclose "primer extension oligonucleotides" for use in their methods in which the 3' termini of the oligonucleotides are

"complementary to the nucleotide located immediately adjacent to the polymorphism site" (see, e.g., pages 18 and 22-23, and claim 4). In these methods of Anastasio et al, isolated nucleic acids from an individual are amplified, and primer extension is performed on the amplified nucleic acids, wherein the identity of the terminator in the extended oligonucleotide is identified to determine the identity of the polymorphism(s) present (see, e.g., claim 4). While Anastasio et al do not refer to the use of "distinctively labeled ddNTPs" in their methods (as set forth in independent claim 1), Anastasio et al do disclose the use of the "polymerase-mediated primer extension method" of patent WO92/15712 (Goelet et al) in the identification of polymorphisms (page 23). Goelet et al teach that their method employs differently labeled terminators, such that the identification of the nucleotide at the position of interest may be established based on the identity of the detectable marker incorporated into the primer during extension (see entire reference, particularly pages 10-13 and 21-22, summarizing the primer extension method of Goelet et al). Thus, the Goelet et al reference provides evidence of the steps and reagents involved in the primer extension method of Anastasio et al. It is further noted that the method of Goelet et al (i.e., the method referenced in the Anastasio et al reference) requires identification of the detectable marker present on the terminator incorporated during primer extension (see, e.g., pages 11 and 22), and that Goelet et al teach subjecting labeled, extended primers to polyacrylamide gel electrophoresis (see, e.g., page 38 and 43).

With further regard to claim 23, which depends from amended claim 19, the claims as amended merely require identification of "at least one polymorphism" using "at

least one labeled extension primer," such that the claims broadly encompass methods in which the steps of the claims are practiced to achieve identification of only a single polymorphism. However, it is noted that Anastasio et al disclose the practice of primer extension assays on arrays in order to detect multiple polymorphisms "at the same time" (see page 19), as well as the use of sets of primer pairs to assay multiple polymorphic sites by primer extension (see page 22), and the investigation of "multiple polymorphic sites...simultaneously" (page 23). Further, Goelet et al disclose that primer extension involves the use of 4 differently labeled ddNTPs (see page 11), and also provide teachings of how primer extension may be performed to analyze "one or more specified positions" wherein "different positions can be determined simultaneously" (see, page 12, as well as pages 31-33). With regard to the method step requiring size separation and "using the length of the labeled extension primer and the identity of its distinctively labeled ddNTP to identify at least one polymorphism" (see text of claim 19), Goelet et al further teach that their method encompasses subjecting labeled, extended primers to polyacrylamide gel electrophoresis (see, e.g., page 38 and 43), such that the method of Anastasio et al in light of Goelet et al would inherently include steps meeting the requirements of claim 19 (and further, it is again noted that the identification of only a single polymorphism is sufficient to meet the requirements of the claims, such that no actual teaching of the differentiation of the lengths of various products is actually required).

However, the Anastasio et al reference in light of the Goelet et al reference does not teach the use of capillary electrophoresis, as required by the instant claims.

Dovichi and Zhang teach that capillary electrophoresis (CE) allows for the more rapid determination of a DNA sequence as compared to conventional polyacrylamide gel electrophoresis (PAGE)(see entire reference, particularly pages 227-228). In view of the teachings of Dovichi and Zhang, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Anastasio et al so as to have subjected extended primers to CE rather than PAGE. An ordinary artisan would have been motivated to have made such a modification for the advantage of more rapidly determining the terminal base present in extended primers, as suggested by the teachings of Dovichi and Zhang.

With regard to Anastasio et al in light of Goelet et al, **the response traverses the rejection** for the same reasons discussed in paragraph 10, above. Accordingly, the response to those arguments applies equally herein. The response further argues that Dovichi and Zhang do not "cure the deficiencies" of Anastasio et al in light of Goelet et al because the reference fails to provide teachings with regard to P450 2D6 or single nucleotide extension. However, the Dovichi and Zhang reference was not cited to cure any such deficiencies, but was cited merely for its teachings of CE and the advantages thereof, as indicated in the rejection. Accordingly, applicant's arguments are not persuasive.

The combined references of Anastasio et al and Dovichi and Zhang (in light of Goelet et al) suggest all the limitations of present claims 5 and 23, and therefore this rejection is maintained.

13. Claims 10, 28, 36-37, 39, and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anastasio et al in view of Pastinen et al (PCR Applications (1999), pages 521-535; Innis, M.A. et al, editors, Academic Press, San Diego), in light of the teachings of Goelet et al, for the reasons stated below and in the Office action of November 1, 2006. **Applicant's amendments to the claims necessitated any new grounds of rejection set forth herein.**

Anastasio et al disclose methods of genotyping and haplotyping the CYP2D6 gene in which one or more of the polymorphisms present in the gene are detected (see entire reference). Anastasio et al disclose methods in which primer extension is employed to identify polymorphisms, and disclose "primer extension oligonucleotides" for use in their methods in which the 3' termini of the oligonucleotides are "complementary to the nucleotide located immediately adjacent to the polymorphism site" (see, e.g., pages 18 and 22-23, and claim 4). In these methods of Anastasio et al, isolated nucleic acids from an individual are amplified, and primer extension is performed on the amplified nucleic acids, wherein the identity of the terminator in the extended oligonucleotide is identified to determine the identity of the polymorphism(s) present (see, e.g., claim 4). While Anastasio et al do not refer to the use of "distinctively labeled ddNTPs" in their methods (as set forth in independent claim 1), Anastasio et al do disclose the use of the "polymerase-mediated primer extension method" of patent WO92/15712 (Goelet et al) in the identification of polymorphisms (page 23). Goelet et al teach that their method employs differently labeled terminators, such that the identification of the nucleotide at the position of interest may be established based on

the identity of the detectable marker incorporated into the primer during extension (see entire reference, particularly pages 10-13 and 21-22, summarizing the primer extension method of Goelet et al). Thus, the Goelet et al reference provides evidence of the steps and reagents involved in the primer extension method of Anastasio et al.

With further regard to claim 28, which depends from amended claim 19, the claims as amended merely require identification of "at least one polymorphism" using "at least one labeled extension primer," such that the claims broadly encompass methods in which the steps of the claims are practiced to achieve identification of only a single polymorphism. However, it is noted that Anastasio et al disclose the practice of primer extension assays on arrays in order to detect multiple polymorphisms "at the same time" (see page 19), as well as the use of sets of primer pairs to assay multiple polymorphic sites by primer extension (see page 22), and the investigation of "multiple polymorphic sites...simultaneously" (page 23). Further, Goelet et al disclose that primer extension involves the use of 4 differently labeled ddNTPs (see page 11), and also provide teachings of how primer extension may be performed to analyze "one or more specified positions" wherein "different positions can be determined simultaneously" (see, page 12, as well as pages 31-33). With regard to the method step requiring size separation and "using the length of the labeled extension primer and the identity of its distinctively labeled ddNTP to identify at least one polymorphism" (see text of claim 19), Goelet et al further teach that their method encompasses subjecting labeled, extended primers to polyacrylamide gel electrophoresis (see, e.g., page 38 and 43), such that the method of Anastasio et al in light of Goelet et al would inherently include steps meeting

the requirements of claim 19 (and further, it is again noted that the identification of only a single polymorphism is sufficient to meet the requirements of the claims, such that no actual teaching of the differentiation of the lengths of various products is actually required).

Anastasio et al do not teach an extension primer having any of SEQ ID Nos 9-19, as required by the claims. It is again noted that Applicant elected SEQ ID Nos 9, 11, and 14 for examination.

Pastinen et al disclose a method of genotyping the CYP2D6 gene that accomplishes detection of multiple CYP2D6 alleles, including the elected CYP2D6*4 allele, by primer extension (see entire reference, particularly pages 529-530). The primer employed by Pastinen et al in detection of the CYP2D6*4 allele, primer 2D6*4 (see page 530), comprises the sequence identified by applicant as SEQ ID NO: 9.

In view of the teachings of Pastinen et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the primer extension method of Anastasio et al so as to have employed therein the 2D6*4 primer of Pastinen et al in embodiments of the method in which the detection of CYP2D6*4 was desired. As Anastasio et al do not exemplify detection of this allele using primer extension, and as Pastinen et al exemplify the successful use of their primer in detection the CYP2D6*4 allele, an ordinary artisan would have been motivated to have made such a modification (as opposed to, e.g., experimenting with various primers in order to identify an appropriate primer) for the advantage of more rapidly and conveniently achieving detection of CYP2D6*4.

With regard to Anastasio et al in light of Goelet et al, **the response traverses the rejection** for the same reasons discussed in paragraph 10, above. Accordingly, the response to those arguments applies equally herein. The response further argues that Pastinen et al do not "cure the deficiencies" of Anastasio et al in light of Goelet et al because the reference fails to provide teachings with regard to "a single reaction with multiple extension primers with distinctively labeled ddNTPs." However, the Pastinen et al reference was not cited to cure any such deficiencies, but was cited rather for its teachings with regard to SEQ ID NO: 9 and its utility in detecting the CYP2D6*4 allele. The response further argues that Pastinen "teaches away from using distinctively labeled ddNTPs...by stating that multiple labels would not increase capacity compared to Pastinen's disclosed method" (citing page 532, lines 24-31). However, this teaching of Pastinen et al pertains to Pastinen et al's method as compared to another minisequencing method known in the prior art; the instant rejection does not rely on Pastinen et al for its teachings with regard to general methodology, but rather for its teaching of a specific sequence useful in detecting a particular CYP2D6 allele. The practice of the method of Anastasio et al (as discussed previously) inherently employs distinctively labeled ddNTPs, and nothing in the Pastinen et al reference teaches away from the use of such ddNTPs in Anastasio et al's primer extension method for CYP2D6 genotyping/haplotyping. Finally, the response argues that one of skill in the art "would not be motivated to alter the primer [of Pastinen et al] by more than two bases," such that it would not be obvious to arrive at SEQ ID NO:9 of the instant claims. However, as noted above (and in the original rejection), the primer of Pastinen et al in fact includes

SEQ ID NO: 9 in its entirety, and applicant's claims as written are not limited to, e.g., a primer "consisting of" this sequence, but rather are sufficiently broad so as to encompass primers including it. Thus, applicant's arguments are not persuasive.

The combined references of Anastasio et al and Pastinen et al (in light of Goelet et al) suggest all the limitations of present claims 10, 28, 36-37, 39, and 41-42, and therefore this rejection is maintained.

14. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anastasio et al in view of Pastinen et al, in light of the teachings of Goelet et al, as applied to claims 10, 28, 36-37, 39, and 41-42, above, and further in view of Dovichi and Zhang, for the reasons stated below and in the Office action of November 1, 2006.

It is further noted that the method of Goelet et al (i.e., the method referenced in the Anastasio et al reference) requires identification of the detectable marker present on the terminator incorporated during primer extension (see, e.g., pages 11 and 22), and that Goelet et al teach subjecting labeled, extended primers to polyacrylamide gel electrophoresis (see, e.g., page 38 and 43). However, Anastasio et al and Pastinen et al, in light of the Goelet et al reference, do not teach the use of capillary electrophoresis, as required by the instant claims.

Dovichi and Zhang teach that capillary electrophoresis (CE) allows for the more rapid determination of a DNA sequence as compared to conventional polyacrylamide gel electrophoresis (PAGE)(see entire reference, particularly pages 227-228). In view of the teachings of Dovichi and Zhang, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method

of Anastasio et al in view of Pastinen et al so as to have subjected extended primers to CE rather than PAGE. An ordinary artisan would have been motivated to have made such a modification for the advantage of more rapidly determining the terminal base present in extended primers, as suggested by the teachings of Dovichi and Zhang.

With regard to Anastasio et al, Pastinen et al, and Goelet et al, **the response traverses the rejection** for the same reasons discussed in paragraphs 10 and 13, above. Accordingly, the response to those arguments applies equally herein. The response further argues that Dovichi and Zhang do not "cure the deficiencies" of Anastasio et al and Pastinen et al in light of Goelet et al because the reference fails to provide teachings with regard to P450 2D6 or single nucleotide extension. However, the Dovichi and Zhang reference was not cited to cure any such deficiencies, but was cited merely for its teachings of CE and the advantages thereof, as indicated in the rejection. Accordingly, applicant's arguments are not persuasive.

The combined references of Anastasio et al and Pastinen et al (in light of Goelet et al) and Dovinchi and Zhang suggest all the limitations of present claim 40, and therefore this rejection is maintained.

Allowable Subject Matter

15. Claim 3 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Diana B. Johannsen
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Art Unit 1634